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Short-term Morbidity and Ipsilateral Breast Tumor Recurrence Associated to Nipple/ Skin Sparing Mastectomy with Immediate Reconstruction

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Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

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Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Cirurgia

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Subareolar unilateral and bilateral breast trauma Recurrence associated to nipple/areolar sparing Mastectomy with immediate reconstruction

ORIENTADOR

José Luís Fonseca

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Faculdade de Medicina da Universidade do Porto, 22/03/2019

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It always seems impossible until it's done- Nelson Mandela.

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Short Term Morbidity and Ipsilateral Breast Tumor Recurrence Associated to Nipple/Skin Sparing Mastectomy with Immediate Reconstruction

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Abbreviations:

ANED, alive with no evidence of disease
AWC, alive with cancer
BC-CHSJ, Breast Centre of São João University Hospital
BCS, breast-conserving surgery
BMI body mass index
CDC, Clavien-Dindo Classification
CHUSJ, São João University Hospital
CS, Current Status
CT, computed tomography
ChT, Chemotherapy
DI, Direct to Implant
DIEP, Deep inferior epigastric artery perforator
DOC, died of cancer
DOTHER, died of another reason
ER, estrogen receptor
FEC, 5-fluorouracil-epirubicin-cyclophosphamide
HER2, Human epidermal growth factor receptor-2
HT, hormonal therapy
IBR, immediate breast reconstruction
IHC, Immunohistochemistry
ISH, In situ hybridization
LD, Latissimus Dorsi
LN, lymph node
LR, local recurrence
NSABP, National Surgical Adjuvant Breast and Bowel Project
NSM, nipple-sparing mastectomy
NST, No special type
OPBC, Oncoplastic Breast Consortium
PR, progesterone receptor
PT, Primary Tumor
RATFS, retroareolar tissue frozen section
RT, Radiotherapy
SSM, skin-sparing mastectomy
TC, temozolomide and capecitabine
TE, Tissue Expander
TRAM, Transverse Rectus Myocutaneous
UIQ, Upper-Inner Quadrant of breast
UOQ, Upper-Outer Quadrant of breast
Yo, years-old

Abstract

Background: In 2018, an estimated 2.1 million new cases of breast cancer were detected in women worldwide, making it the most commonly diagnosed cancer among females. Skin-Sparing Mastectomy (SSM) and Nipple-Sparing Mastectomy (NSM) are surgical treatment options, but are still faced with some degree of concern regarding their oncological safety and their immediate complications following surgery. In order to add up to already available consecutive case series on the subject, this paper aims to give information on the type and rate of immediate surgical morbidity (within 30 days), local tumor recurrence and the occurrence of new primary breast cancer following risk-reducing SSM/NSM.

Methods: Retrospective analysis of clinical files of patients who underwent SSM or NSM with immediate breast reconstruction at the BC-CHSJ between January 2011 and December 2015.

Results: A total of 186 patients underwent SSM or NSM followed by IBR at CHUSJ Breast Centre between January 2011 and December 2015. Of these, 46 underwent double mastectomy, resulting in a total of 232 surgical procedures. Overall complication rate was 42,2%, and the rate of grade II/III complications using the Clavien-Dindo Classification was 27.1%. Local recurrence rate of breast cancer following these procedures was 1.8% over a 56-months (range, 13-93) follow-up. No cases of primary tumor following prophylactic surgery were reported.

Conclusions: The rate of immediate complications with an impact in patient's clinical course following skin-sparing or nipple sparing mastectomy is low. Recurrence rate following these procedures is comparable to that of traditional mastectomy and after prophylactic procedures there were no primary breast tumors detected.

INTRODUCTION

In 2018, an estimated 2.1 million new cases of breast cancer were detected in women worldwide, making it the most commonly diagnosed cancer among females (11.6% of the total cases).[1] Breast cancer is the leading cause of cancer death among women as well, and its complex approach requires a multi-disciplinary team of professionals consisting of oncologic and plastic surgeons, radiologists, oncologists, pathologists and expertise of other fields, such as Psychology and Nursing.[1,2]

The publishing of the Milan trials in 1981 and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial in 1985 was considered a landmark, for such projects paved the way for the emergence of breast-conserving surgery (BCS)- quadrantectomy or lumpectomy.[3,4] These techniques are less mutilating than it had been previously assumed to be necessary for breast cancer treatment, originating a paradigm shift for the surgical management of breast cancer.[3,4] Nowadays, aesthetic results are a matter under growing awareness in the management of breast cancer due to the psychological effects caused by breast disfigurement.[5,6] As a result, despite oncological safety being the main focus of treatment, a present-day operation gracefully balances disease control with external appearance outcomes, fitting within the concept of oncoplastic surgery.[7] Nevertheless, about one-third of women with breast cancer still require a mastectomy, either because BCS is declined or due to the size, site or extent of the tumor.[8]

Skin-Sparing Mastectomy (SSM) and Nipple-Sparing Mastectomy (NSM) are of comparatively recent vintage, rising to surface along the lines of the change in the paradigm.[9] Indeed, in 1962, Freeman introduced a subcutaneous mastectomy for benign breast lesions with immediate or delayed prosthetic replacement, and five years later he described its complications.[10,11] In order to avoid the complications of immediate reconstruction, surgeons then started to adopt a technique in which the nipple would be transplanted to the groin and kept there until the final breast reconstruction, which in turn led to reports describing the development of infiltrating carcinoma at the transplantation site, bringing about the disuse of free nipple grafting in oncologic surgeries by most surgeons for many years.[12,13] In 1991, the term “skin-sparing mastectomy” was used for the first time by Toth and Lappert, and a few years later, despite the opposing views of some analyses, the concept of NSM was revisited in the context of breast surgical oncology, after the results of the NSABP B-06 study- a randomized, prospective, multicenter study, with 20 years of published follow-up- reported no difference in survival among the patients randomized to mastectomy, lumpectomy or lumpectomy with radiation therapy.[4, 14-19] Jensen points out that safety of NSM is sustained on the fact that, in the face of a nipple recurrence, the patient can be treated without loss of benefit in survival, and not on the assumption that it is not possible for nipple recurrences to occur.[20-23] The Oncoplastic Breast Consortium consensus conference panel held in 2018, consisting of 44 breast surgeons and a patient advocate, regards NSM as a safe procedure, if patients meet the recommended criteria and appropriate techniques are performed by a team of specialists.[24]

On account on some concern still present on the oncological safety of SSM and NSM, and to add up to consecutive case series on the subject already available, in addition to characterizing the patients who underwent SSM or NSM with immediate breast reconstruction (IBR) in the Breast Centre of São

João University Hospital (BC-CHSJ) from January 2011 to December 2015, this paper aims to give information on the type and rate of immediate surgical morbidity (within 30 days), local tumor recurrence and the occurrence of new primary breast cancer following risk-reducing SSM/NSM.

METHODS

Patient and procedure data

All patients who underwent SSM or NSM with IBR at the BC-CHSJ between January 2011 and December 2015 were identified using a retrospective surgery chart review. Patients on this chart were assigned to SSM or NSM by their physician, based on the diagnosis of breast cancer or the identification of oncogenic mutations with increased risk for breast cancer development. SSM was performed if the tumor or the suspicious microcalcifications were within a 10mm distance from the nipple. In case they were more than 20mm away from the nipple, NSM would be the chosen option. Retroareolar tissue frozen section was performed in the cases in which the tumor or the suspicious microcalcifications were within a 10-20 mm range from the nipple. In the event of a positive RATFS result, NAC excision was performed. The medical files of all selected patients were then retrospectively reviewed, and a database was created.

Collected patient data included age at diagnosis and age at surgery, date of last medical observation, weight (kg), height (cm), smoking habits and the need for adjuvant treatments. Regarding tumor features, final pathologic stage, histologic grade, the presence of lymphovascular invasion, the histological subtype, the status of estrogen receptor (ER), progesterone receptor (PR) and Human epidermal growth factor receptor-2 (HER2) protein overexpression were recorded. ER and PR were deemed positive if present in at least 1% of the tumor cells. HER-2 was considered positive in cases of IHC +++ or ISH positivity. Tumor staging was performed according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th Edition. Surgical data included mastectomy technique and the reconstruction technique, previous or simultaneous sentinel LN biopsy, and the performance and outcomes of retroareolar tissue frozen section (RATFS).

Immediate surgical morbidity included explantation of prosthesis, hematoma, seroma, partial and total nipple/areola necrosis, wound infection, skin flap necrosis, distant flap necrosis (LD, TRAM, DIEP), wound dehiscence, rehospitalization and reoperation rates (30 days). Complications were graded according to the Clavien-Dindo classification.[25] Date and site of first local recurrence (LR) was also analyzed.

After mastectomy, patient's follow-up differed according to tumor stage: stages 1 and 2 were submitted to yearly physical examination, mammography and breast ultrasound; in addition, stages 3 and 4 performed yearly bone scintigraphy, total CT scan and serum tumor markers measurements (CEA and Ca15.3).

This study was approved by the Ethics Committee of CHUSJ.

Statistical analysis

Descriptive statistical analysis was performed using IBM SPSS Statistics 24.0 (SPSS Inc., Chicago, IL, USA).

Rate of immediate complications was calculated by dividing the number of procedures in which a complication occurred in the 30 days following surgery by the total number of procedures. Rate of LR was calculated by dividing the number of recurrences by the total number of procedures with a curative purpose. Rehospitalization rate was calculated by dividing the number of individuals who were readmitted to the hospital in the next 30 days after surgery by the total number of individuals that underwent SSM/NSM.

RESULTS

Patient and Surgery Characteristics

A total of 186 patients underwent SSM or NSM followed by IBR at CHUSJ Breast Centre between January 2011 and December 2015. Of these, 46 underwent double mastectomy, resulting in a total of 232 surgical procedures.

Median age at diagnosis was 48yo (range, 26-80), with a median BMI of 24,7 kg/m^2 and a 15.6% smoking rate (Table 1). Median waiting time for elective surgery was 47 days (range, 1-2723). The vast majority of patients (91,9%) are currently alive with no evidence of cancer. One patient presented with synchronous hepatic metastases at primary diagnosis of breast cancer and later died of the disease. A large number of patients had stage 0 breast cancer (21,5%), stage 1 cancer (30,6%) or stage 2 cancer (22,0%). Among those with invasive cancer, 88,9% and 79,8% showed positivity for estrogen receptors and progesterone receptors, respectively, and 16.2% had HER2 protein overexpression. In addition, considering that group, the majority underwent adjuvant ChT or endocrine therapy, while only 10,1% received radiation therapy.

More than half of surgical procedures were performed with a curative purpose (163, 70,3%), whereas 69 (29,7%) presented as a risk-reducing surgery (Table 2). A total of 86 SSM and 146 NSM were performed. Only 62 charts clearly stated the adopted surgical excision technique, the most used being blade dissection alone (40 procedures). Mixed excision technique were defined as a combination of sharp dissection and/or scissors and/or electrocautery. The most frequent breast reconstruction techniques were subpectoral expander (two stages technique, 44,8%) and TRAM-flap (23,3%). Surgeons performed 43 RATFS (18,5% of procedures), 10 of which resulted in the detection of a tumor. In those cases, the surgeon proceeded to NAC excision.

TABLE 1. PATIENT CHARACTERISTICS

		Total (n=232)	SSM (n=86)	NSM (n=146)	Curative (n=163)	Risk-reducing (n=69)
Median age at diagnosis, years (n=186)		48 (26-80)	51 (35-80)	46 (26-68)	49 (26-80)	41 (26-72)
Median waiting time, days (n=186)		47 (1-2736)	42 (2-547)	52 (1-2736)	42 (1-383)	95 (18-2736)
Median follow-up time, months (n=186)		52 (13-93)	52 (13-93)	55 (16-91)	55 (16-93)	51 (13-91)
Current Status (n=186)	ANED	171 (91,9%)	67 (90,5%)	104 (92,9%)	128 (92,1%)	46 (97,9%)
	AWC	13 (7,0%)	6 (8,1%)	7 (6,3%)	10 (7,2%)	-
	DOC	1 (0,5%)	1 (1,4%)	-	1 (0,7%)	-
	DOTHER	1 (0,5%)	-	1 (0,9%)	-	1 (2,1%)
Weight median, kg (n=182)		63 (44-93)	64 (44-89)	64 (45-93)	64 (44-89)	63 (47-93)
Height, median, cm (n=162)		160 (134-178)	160 (134-175)	161 (146-178)	160 (134-178)	162 (142-175)
BMI, median (n=162)		24,7 (16,7-38,1)	25,3 (17,3-34,3)	24,1 (16,7-38,1)	24,8 (16,7-34,3)	24,0 (17,3-38,1)
Smoking habits (n=186)	no	115 (61,8%)	43 (58,1%)	72 (64,3%)	87 (62,6%)	28 (59,6%)
	yes	29 (15,6%)	11 (14,9%)	12 (16,1%)	23 (16,5%)	6 (12,8%)
	unknown	42 (22,6%)	20 (27,0%)	22 (19,6%)	29 (20,9%)	13 (27,7%)
Stage of cancer (n=186)	0	40 (21,5%)	18 (24,3%)	22 (19,6%)	40 (28,8%)	-
	1	57 (30,6%)	26 (35,1%)	31 (27,7%)	57 (41,0%)	-
	2	41 (22,0%)	18 (24,3%)	23 (20,5%)	41 (29,5%)	-
	4	1 (0,5%)	1 (1,4%)	-	1 (0,7%)	-
	NA	47 (25,3%)	11 (14,9%)	36 (32,1%)	-	47 (100%)
Tumor grade (invasive cancer n=99)	1	28 (28,3%)	14 (31,1%)	14 (25,9%)	28 (28,3%)	-
	2	41 (41,4%)	20 (44,4%)	21 (38,9%)	41 (41,4%)	-
	3	28 (28,3%)	13 (15,1%)	17 (31,5%)	28 (28,3%)	-
	NA	2 (2%)	-	2 (3,8%)	2 (2,0%)	-
LN metastasis (invasive cancer n=99)	no	86 (86,9%)	37 (82,2%)	49 (90,7%)	86 (86,9%)	-
	yes	13 (13,1%)	8 (17,8%)	5 (9,3%)	13 (13,1%)	-
ER (invasive cancer n=99)	negative	11 (11,1%)	4 (8,9%)	7 (13,0%)	11 (11,1%)	-
	positive	88 (88,9%)	41 (91,1%)	47 (87,0%)	88 (88,9%)	-
PR (invasive cancer n=99)	negative	20 (20,2%)	6 (13,3%)	14 (25,9%)	20 (20,2%)	-
	positive	79 (79,8%)	39 (86,7%)	40 (74,1%)	79 (79,8%)	-
HER2 status (invasive cancer n=99)	negative	81 (81,8%)	34 (75,6%)	47 (87,0%)	81 (81,8%)	-
	positive	16	10	6	16	-

		(16,2%)	(22,2%)	(11,1%)	(16,2%)	
	Undefined	2 (2,0%)	1 (2,2%)	1 (1,9%)	2 (2,0%)	-
Chemotherapy (invasive cancer n=99)	no	41 (41,4%)	19 (42,2%)	22 (40,7%)	41 (41,4%)	-
	neoadjuvant	2 (2,0%)	-	2 (3,7%)	2 (2,0%)	-
	adjuvant	56 (56,6%)	26 (57,8%)	30 (55,6%)	56 (56,6%)	-
Radiation therapy (invasive cancer n=99)	no	89 (89,9%)	38 (84,4%)	51 (94,4%)	89 (89,9%)	-
	yes	10 (10,1%)	7 (15,6%)	3 (5,6%)	10 (10,1%)	-
Antihormonal therapy (invasive cancer n=99)	no	10 (10,1%)	2 (4,4%)	8 (14,8%)	10 (10,1%)	-
	adjuvant	89 (89,9%)	43 (95,6%)	46 (85,2%)	89 (89,9%)	-

ANED= alive with no evidence of cancer, AWC= alive with cancer, BMI= body mass index; DOTHER= died of other reason, ER= estrogen receptor, HER2= human epidermal growth factor receptor-2, LN= lymph node, DOC=died of cancer, PR= progesterone receptor

TABLE 2. SURGERY CHARACTERISTICS

		Total (n=232)	SSM (n=86)	NSM (n=146)	Curative (n=163)	Risk-Reducing (n=69)
Mastectomy technique	Tumescent technique+ Sharp dissection alone	1 (0,4%)	-	1 (0,7%)	1 (0,6%)	-
	Blade dissection alone	40 (17,2%)	17 (19,8%)	23 (15,8%)	29 (17,8%)	11 (15,9%)
	Scissors dissection alone	7 (3,0%)	2 (2,3%)	5 (3,4%)	6 (3,7%)	1 (1,4%)
	Electric cautery alone	-	-	-	-	-
	Mixed technique	13 (5,6%)	3 (3,5%)	10 (6,8%)	10 (6,1%)	3 (4,3%)
	Unknown	170 (73,3%)	22 (25,6%)	110 (75,3%)	117 (71,8%)	54 (78,2%)
Type of reconstruction	Subpectoral TE	104 (44,8%)	32 (37,2%)	72 (49,3%)	59 (36,2%)	45 (65,2%)
	Prepectoral TE	3 (1,3%)	-	3 (2,1%)	2 (1,2%)	1 (1,4%)
	Subpectoral DI	28 (12,1%)	4 (4,7%)	24 (16,4%)	16 (9,8%)	12 (17,4%)
	Prepectoral DI	3 (1,3%)	-	3 (2,1%)	-	3 (4,3%)
	LD + Implant	19 (8,2%)	12 (14%)	7 (4,8%)	18 (11%)	1 (1,4%)
	Skin Graft + Implant	2 (0,9%)	-	2 (1,4%)	2 (1,2%)	-
	TRAM Flap	54 (23,3%)	26 (30,2%)	28 (19,2%)	49 (30,1%)	5 (7,2%)
	DIEP Flap	18 (7,8%)	12 (14,0%)	6 (4,1%)	16 (9,8%)	2 (2,9%)
	LD + Expander	1 (0,4%)	-	1 (0,7%)	1 (0,6%)	-

DI= Direct to Implant, DIEP= Deep inferior epigastric artery perforator, LD= Latissimus Dorsi, TE= Tissue Expander, TRAM= Transverse Rectus Myocutaneous

Immediate complications

Information regarding the morbidity events in the 30 days following surgery was easily available in all clinical files, except for one patient's file, which did not have sufficient data for assessment of surgical morbidity.

Overall complication rate was 42,2%, and the rate of grade II/III complications using the Clavien-Dindo Classification was 27.1% (Table 3). The most frequent immediate complication after mastectomy was the development of a hematoma (12,9%). The vast majority of the patients (72,8%) suffered no complications or minor, grade I. Serious complications (e.g., CDC grade III) occurred after 13,8% of procedures. Partial and total nipple/ areolar necrosis happened in 14.8% and 8.5% of NSMs, respectively.

Re-hospitalization rate was 5,4% (10/186) and 15,6% of patients were re-operated under general anesthesia.

TABLE 3. IMMEDIATE COMPLICATIONS (30 DAYS)

		Total (n=232)	SSM (n=86)	NSM (n=146)	Curative (n=163)	Risk-reducing (n=69)
Immediate Complications						
Explantation of prosthesis		8 (3,4%)	4 (4,7%)	4 (12,3%)	5 (3,1%)	3 (4,3%)
Hematoma		30 (12,9%)	12 (14,0%)	18 (12,3%)	25 (15,3%)	5 (7,2%)
Seroma		25 (10,8%)	14 (16,3%)	11 (7,5%)	18 (11,0%)	7 (10,1%)
Partial nipple/ areolar necrosis		24 (10,3%)	-	24 (16,4%)	15 (9,2%)	9 (13,0%)
Total nipple/ areolar necrosis		13 (5,6%)	-	13 (8,9%)	7 (4,3%)	6 (8,7%)
Wound infection		10 (4,3%)	6 (7%)	4 (2,7%)	9 (5,5%)	1 (1,4%)
Skin flap necrosis		20 (8,6%)	11 (12,8%)	9 (6,2%)	15 (9,2%)	5 (7,2%)
Distant flap necrosis (LD, TRAM, DIEP)		9 (3,9%)	6 (7,0%)	2 (2,1%)	9 (5,5%)	-
Wound dehiscence		14 (6,0%)	10 (11,6%)	2 (2,7%)	12 (7,4%)	2 (2,9%)
Others						
Rehospitalization (30 days)						
Reoperation under general anesthesia						
Clavien-Dindo Classification						
	0-I	169 (72,8%)	58 (67,4%)	111 (76,0%)	116 (71,2%)	53 (76,8%)
	II	31 (13,4%)	15 (17,4%)	16 (11,0%)	24 (14,7%)	7 (10,1%)
	III (A/B)	32 (13,8%)	13 (15,1%)	19 (13,0%)	23 (14,1%)	9 (13,0%)
Nº Procedures with complications				**98**		
Overall Complication Rate				**42,2%**		
Grade II/III Complications Rate				**27,1%**		
Rehospitalization rate (30 days)				**5,4%**		

DIEP= Deep inferior epigastric artery perforator, LD= Latissimus Dorsi, TRAM= Transverse Rectus Myocutaneous

Local recurrence and Primary Tumor after Prophylactic Mastectomy

Three of a total of 163 SSM/NSM with a curative purpose had breast cancer recurrence (Table 4). Therefore, LR rate of breast cancer following these procedures was 1.8% over a 56-months (range, 13-93) follow-up. The median time from treatment to LR was 36 months (mean, 36,7; range, 29-45).

In 2011, patient A underwent bilateral NSM with IBR with expanders and subsequent adjuvant ChT (FEC) and HT (tamoxifen) for a right breast primary tumor. Definitive 355cc implants placed in 2012 were later switched to 435cc implants in 2015, both procedures followed one year later by breast augmentation by lipofilling. In 2017, this patient underwent total mastectomy of the right breast and sentinel LN biopsy. Pathology described a multifocal in-breast recurrence (4 foci, sized from 8 to 14 mm). Then, Patient A received ChT (TC*6), thoracic wall RT and HT (exemestane).

Patient B underwent NSM of the left breast with IBR with DIEP flap in 2011, followed by adjuvant ChT (FEC) and HT (tamoxifen). Subcutaneous LR was diagnosed in 2015, and prompted a tumorectomy plus sentinel node biopsy, and adjuvant breast RT and HT with anastrozole.

In January 2015, patient C was diagnosed with a 9mm tumor in the right breast. This patient had a 16,8 kg/m^2 BMI and an A breast cup. NSM with IBR with a 245cc implant took place in February 2015, and a week later patient was re-operated due to hematoma and maintained the implant. This patient received 2 cycles of adjuvant TC and later switched to 4 cycles of AC due to multiple systemic reactions to TC. In 2016, implant was switched to a 320 cc one and a lipofilling was performed. In 2017, excision of a cutaneous node on the mastectomy scar revealed a local tumor recurrence. This resulted in a total mastectomy and adjuvant chest wall RT and 8 cycles of capecitabine.

No cases of primary breast cancer were detected after prophylactic mastectomy.

TABLE 4. PATIENTS WITH LOCAL RECURRENCE

	PT: Site, Surgery, Characteristics and Adjuvant therapy	**PT treatment-to-recurrence interval**	**Recurrence: Site, Surgery, Treatment**	**CS and Follow-up time**
Patient A	UOQ, NSM with underpectoral expander, Multifocal Mixed tumor (ductal and mucinous). HR+ (>80%), Her2- pT2 (14mm) N0sn M0 G3 R0 ChT+HT+RT	73 months	UOQ, Subcutaneous/ in-breast, Total Mastectomy (including reconstruction) ChT+RT+HT	ANED 92 months
Patient B	UIQ, NSM with DIEP flap, Unifocal NST carcinoma. HR+ (>90%) HER2- pT2 (22mm) N0sn M0 G2 R0 ChT+ HT	44 months	UIQ, Subcutaneous/ in-breast, Wide Excision + RT+ HT	ANED 82 months
Patient C	UIQ, NSM with underpectoral implant, Unifocal Basal cell carcinoma HR- Her2- pT1 (8mm) N0sn M0 G3 R0 ChT+ RT	28 months	UIQ, Cutaneous (Surgical Scar), Total Mastectomy (including reconstruction) RT + ChT	ANED 54 months

CS= Current Status, ChT= Chemotherapy, HT= hormonal therapy, NST= No special type, PT= Primary Tumor, RT= Radiotherapy, UIQ= Upper-Inner Quadrant of breast cancer UOQ= Upper-Outer Quadrant of breast cancer

DISCUSSION

Authors of this study carried out a retrospective review of patient's clinical files to examine the complications and the oncological safety of SSM/NSM with IBR. In skin-sparing mastectomy, the breast glandular tissue is removed and separated from the subcutaneous fat, but most of the breast skin is retained.[9] Nipple-sparing mastectomy is in essence the same process, with the exception of the conservation of the nipple-areolar complex.[9] During the surgery, in case the retroareolar tissue sent for frozen pathology reports the presence of a tumor, the surgeon proceeds to excision of the nipple areolar complex.[2]

Immediate complications associated with the analyzed conservative mastectomies included breast prosthesis explantation, hematoma, seroma, wound infection or dehiscence, necrosis (nipple, skin-flap, or distant flap necrosis). Rehospitalization and reoperation under general anesthesia were also taken into account in this analysis. The overall complication rate was 42,2%. However, considering the complications that authors of this study find to have a bigger impact on patient's well-being and clinical course (eg Clavien-Dindo grade II/III complications), this rate was 27,1%, which is close to those reported in literature.[26] Nipple necrosis rate was 15,9%**.** A systematic review of the literature from Headon et which included 12 358 NSMs and revealed an overall complication rate of 22.3% and overall incidence of partial or total nipple necrosis of 5.9%.[26] Partial or full nipple necrosis is reported in 2% to 20% of cases after NSMs.[27] Headon et al. suggested that factors that influence the occurrence of nipple necrosis were breast features (large size and ptosis), periareolar incision, tobacco use and re-exposure to radiotherapy.[26]

Local recurrence rate of breast cancer following skin-sparing or nipple-sparing mastectomy with immediate breast reconstruction was 1.8% over a 56-months follow-up. This indicates that these procedures present as an oncologically safe option for patients that meet the criteria for such procedures. Earlier studies reviewed SSM with IBM and found LR rates equivalent to those of total mastectomy and that ranged from 0% to 8.3%.[5, 28-31] Likewise, De La Cruz et al. authored a meta-analysis and systematic review that included 5594 patients and concluded that NSM and SSM was not associated with higher LR rates compared to modified radical mastectomy.[32] In fact, Mota et al states describes that after a traditional mastectomy, there is a 2.3% likelihood after 20 years of breast cancer having a LR.[33] Several factors influence the risk of LR after SSM/NSM, including T2/T3 cancer, triple negative tumors, high-grade tumors and positive lymph nodes.[31] Vaughan et al. reported that 82% of patients had local recurrence in the same area as the primary tumor.[30] This work had similar findings. Specifically, LR mainly occurred subcutaneously and one cutaneous recurrence, and the area of recurrence was the same as that of the primary tumor.

The greatest limitation of this study was the quality of the reporting of complications following mastectomy. Each physician adopted different ways of writing patient's reports, and its interpretation may have affected the results. The nearly five-year follow-up is also a limitation, and future studies with longer follow-ups are advised for better assessment of oncologic outcomes of NSM/ SSM.

This study found no cases of primary breast cancer after risk-reducing NSM/SSM. A systematic review published by Carbine et al. reports that both bilateral and contralateral risk-reducing mastectomies are effective in reducing the incidence of breast-cancer, but recommend the future publications of more prospective studies.

In view of these data, the results of this work suggest that SSM and NSM with immediate breast reconstruction present as a feasible option for patients that meet the indication criteria in regards to oncological safety and immediate complications.[24]

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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ANNEX

Porto Biomedical Journal - Instructions for Authors

Note: These instructions comply with those formulated by the International Committee of Medical Journal Editors (ICMJE). For further details, authors should consult the following article: International Committee of Medical Journal Editors. "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" *New Engl J Med* 1997, 336:309–315. The complete document appears at http://www.icmje.org. Manuscripts that do not comply with these Instructions cannot be considered for publication and will be sent back to the authors.

The Editorial Office is pleased to answer any questions you may have about preparing your manuscript in accordance with our guidelines.

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SCOPE

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In addition, to ensure the quality and scientific relevance of PBJ, the journal counts with a diversified and international editorial board, and only accepts original research and review articles that undergo a strict revision process in a double-blind refereeing system, a procedure that safeguards the fairness of the article selection process.

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Any change in authorship/contributions after submission must be approved in writing by all authors and submitted to the Editorial Office for final consideration.

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Authors who are not native speakers of English who submit manuscripts to international journals often receive negative comments from referees or editors about the English-language usage in their manuscripts, and these problems can contribute to a decision to reject a paper. To help reduce the possibility of such problems, we encourage such authors to consider using Wolters Kluwer Author Services*.

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All articles dealing with original human or animal data must include a statement on ethics approval at the beginning of the Methods section. This paragraph must contain the following information: the name and address of the ethics committee responsible; the protocol number that was attributed by this ethics committee; and the date of approval by the ethics committee.

The paragraph could read, for example:

Ethical approval for this study (Ethical Committee N° NAC 207) was provided by the Ethical Committee NAC of Geneva University Hospitals, Geneva, Switzerland on 12 February 2015.

In addition, for studies or case reports conducted on human participants you must state clearly in the text that you obtained written informed consent from the study participants; please also look at the latest version of the Declaration of Helsinki. Similarly, for experiments involving animals you must state the care of animal and licensing guidelines under which the study was performed and report these in accordance with the ARRIVE (Animals in Research: Reporting In Vivo Experiments) statement. If ethics clearance was not necessary, or if there was any deviation from these standard ethical requests, please state why it was not required. Please note that the editors may ask you to provide evidence of ethical approval. If you have approval from a National Drug Agency (or similar) please state this and provide details, this can be particularly useful when discussing the use of unlicensed drugs.

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The protection of a patient's right to privacy is essential. Please collect and keep copies of patients’ consent forms on which patients or other subjects of your experiments clearly grant permission for the publication of photographs or other material that might identify them. If the consent form for your research did not specifically include this, please obtain it or remove the identifying material.

A statement to the effect that such consent had been obtained must be included in the ‘Methods’ section of your paper. If necessary the Editors may request a copy of any consent forms.

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The European Journal of Anaesthesiology adheres to the guidelines on adequate data reporting that were established by The Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network (http://www.equator-network.org/home/).

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A financial disclosure questionnaire must be completed by the corresponding author and all co-authors at initial submission. Co-authors will receive a link to complete the questionnaire via email. Please

ensure each co-author's email address is properly listed at the 'Add/Edit/Remove Authors' submission step in Editorial Manager, to avoid delays in reaching co-authors.

The primary purpose of the disclosure section is to determine whether authors have received any commercial financial support that could create a conflict of interest. In addition to monetary interests, a potential for conflict of interest can exist whether or not an individual believes that a relationship (such as dual commitments, competing interests, or competing loyalties) affects his or her scientific judgment. Please review ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals at the following link: http://www.icmje.org/conflicts-of-interest.

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These should describe fully, but as concisely as feasible, the results of original clinical, laboratory or biomedical research. *Special note regarding case studies:* Case studies will be considered for publication only in the Letters to the Editor section of the Journal. The average Original Article fills 7 pages in the printed journal, although manuscripts that exceed this may be occasionally accepted for publication at the Editors' discretion. In general, an Original Article should not exceed 3500 words, not including the abstract, figure legends, and references. Abstracts should be 250 words or less. If possible, each figure legend should be held to 60 words or less. Each Original Article may be accompanied by no more than 8 graphic presentations (tables and/or figures)-for example, 3 tables + 5 figures. (Additional text, tables, or figures can be designated as "supplemental" material, which will be included in the PBJS Online Repository. Please note: Original Article manuscripts that are determined to significantly exceed these limits, or that do not include all of the elements listed below, may be returned to the authors for revision prior to review.

Letters to the Editor

Letters to the Editor are brief reports of clinical or laboratory observations, substantiated by controlled data but limited in scope, and without sufficient depth of investigation to qualify as Original Articles. These may include a brief description of a particular condition that provides insights into diagnosis and clinical management or images that impart important clinical information. Like Original Articles, these manuscripts are subject to peer review. A Letter to the Editor must:

1) Be brief. The average Letter to the Editor fills 2 pages in the printed journal, although manuscripts that exceed this may be occasionally accepted for publication at the Editors' discretion. In general, a Letter to the Editor should not exceed 1000 words, not including the figure legend(s) and references. If possible, the figure legend(s) should be held to 60 words or less. Please note: Letter to the Editor manuscripts that are determined to significantly exceed these limits may be returned to the authors for shortening prior to review.

2) Have a short, relevant title. Please see the suggestions that appear above (under "A. Original Articles").

3) Have a complete title page (see section A1).

4) Be accompanied by a short summary that encapsulates the report's findings for a clinically oriented audience (see above).

5) Begin with the salutation "To the Editor:"

6) Close with the author's name(s), academic degree(s), institutions(s), and location(s).

7) Have no more than nine references.

8) List the references as complete bibliographic citations following the closure of the letter (see section above for formatting).

9) Present lists of Key words, as relevant (see sections above).

10) Be limited to a total of 2 figures and/or tables. (Additional figures or tables may be placed in the article's Online Repository; please see the relevant section below.)

Correspondence and replies

Correspondence concerning recent publications in the Journal will be considered for publication and accepted based on their pertinence, their scientific quality, and available space in the Journal. If the correspondence is considered acceptable, a response will be requested from the authors of the referenced PBJ article. Upon review and approval by the Editor, the Correspondence and relevant Reply will both be published together. Both Correspondence and Reply manuscripts must:

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4) List the references as complete bibliographic citations at the end of the letter with the journal article being discussed as the first reference (see section above). The total number of references should be no more than seven. Replies should include the Correspondence to which they are replying as one of the references.

5) Have no more than one graphic presentation (table or figure). (See the section on Graphic Presentations below).

6) Begin with the salutation "To the Editor:" and close with the author's name(s), academic degree(s), institutions(s), and location(s).

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Definitive, in-depth, state-of-the-art reviews of clinical and research subjects. Unsolicited reviews are not generally published in PBJ. Before submitting any unsolicited reviews, please forward an outline to the Editor for consideration.

Systematic reviews and meta-analyses should follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (seehttp://www.prisma-statement.org/). A PRISMA flow diagram (http://www.prisma-statement.org/documents/PRISMA%202009%20flow%20diagram.pdf) should be used to describe the steps of the systematic review, and a complete PRISMA checklist (http://www.prisma-

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Official recommendations from professional organizations on issues related to clinical practice and health care delivery. PBJ is most interested in publishing the primary guideline documents but will also consider synopses of guidelines when the primary document is published elsewhere. Synopses should focus on those issues of most relevance to generalist clinicians. Manuscripts must:

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Abstract. Original articles should include a structured abstract of no more than 300 words using the following headings: Background; Methods; Results; and Conclusions. They should briefly describe, respectively, the problem being addressed in the study, how the study was performed, the salient results, and what the authors conclude from the results. Conventional non-systematic, reviews should include an unstructured abstract of no more than 250 words.

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Methods. Avoid detailed description of previously published methods and cite the appropriate reference. Include appropriate ethical and statistical information.

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Pessayre D, Feldmann G, Haouzi D, Fau D, Moreau A, Neumann M. Hepatocyte apoptosis triggered by natural substances (cytokines, other endogenous molecules and foreign toxins). In Cameron RG, Feuer G (editors): Apoptosis and its Modulation by Drugs. Handbook of Experimental Pharmacology. Berlin: Springer-Verlag; 2000, pp. 59-108.

Electronic articles:

Margolis PA, Stevens R, Bordley WC, Stuart J. From concept to application: the impact of a community-wide intervention to improve the delivery of preventive services to children. Pediatrics [online serial] 2001; 108:e42.

http://www.pediatrics.org/cgi/content/full/108/3/e42. [Accessed 20 September 2001].

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